PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
PP/WT/PH/3282		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/GB99/00966	26/03/1999	27/03/1998

International Patent Classification (IPC) or national classification and IPC
C12Q1/68

Applicant
ISIS INNOVATION LIMITED et al.

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 4 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☒ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
27/10/1999	13.12.99

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INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/GB99/00966

I. Basis of the report

1. This report has been drawn on the basis of (*substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.*):

Description, pages:

1-10 as originally filed

Claims, No.:

1-16 as originally filed

2. The amendments have resulted in the cancellation of:

☐ the description, pages:
☐ the claims, Nos.:
☐ the drawings, sheets:

3. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

4. Additional observations, if necessary:

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims 1-16
	No:	Claims
Inventive step (IS)	Yes:	Claims 1-16
	No:	Claims
Industrial applicability (IA)	Yes:	Claims 1-16
	No:	Claims

2. Citations and explanations

see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

Re Item V

Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

The subject-matter of claims 1-16 appears both novel and inventive over the documents cited in the international search report. Thus, the present claims appear to fulfil the requirements of Articles 33(2) and (3) PCT.

The linkage of an allele situated at a locus in a region of chromosome 4 of up to 1 megabase in length, which region contains the locus D4S3032 and /or D4S2921 with asthma appears not to be disclosed or suggested by the prior art, see e.g. ABRAMSON M ET AL: 'The new asthma genetics and its implications for public health' PUBLIC HEALTH REVIEW, vol. 26, no. 2, February 1998 (1998-02), page 138, Table 2, second line.

Re Item VIII

Certain observations on the international application

Claim 1 should be directed to an "in vitro method" in view of claim 2 and the specification. Claim 12 (page 12, line 15) should read "chromosome 4" in order to comply with Article 6 PCT.

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PCT/GB99/00966

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF THE RECORDING OF A CHANGE

(PCT Rule 92bis.1 and Administrative Instructions, Section 422)

To:

WILKINSON, John, Stephen
Stevens, Hewlett & Perkins
1 Augustine's Place
Bristol BS1 4UD
ROYAUME-UNI

Date of mailing (day/month/year)
03 February 2000 (03.02.00)

Applicant's or agent's file reference
KP/3282 PCT

IMPORTANT NOTIFICATION

International application No.
PCT/GB99/00966

International filing date (day/month/year)
26 March 1999 (26.03.99)

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PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF THE RECORDING OF A CHANGE

(PCT Rule 92bis.1 and Administrative Instructions, Section 422)

To:

WILKINSON, John, Stephen
Stevens, Hewlett & Perkins
1 Augustine's Place
Bristol BS1 4UD
ROYAUME-UNI

Date of mailing (day/month/year)
19 April 2000 (19.04.00)

Applicant's or agent's file reference
KP/3282 PCT

IMPORTANT NOTIFICATION

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PCT/GB99/00966

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26 March 1999 (26.03.99)

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Form PCT/IB/306 (March 1994)

003237937

PCT/GB99/00966

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

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NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

Assistant Commissioner for Patents
United States Patent and Trademark Office
Box PCT
Washington, D.C.20231
ÉTATS-UNIS D'AMÉRIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 02 December 1999 (02.12.99)	
International application No. PCT/GB99/00966	**Applicant's or agent's file reference** KP/3282 PCT
International filing date (day/month/year) 26 March 1999 (26.03.99)	**Priority date** (day/month/year) 27 March 1998 (27.03.98)
Applicant COOKSON, William, Osmond, Charles, Michael et al	

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International Preliminary Examining Authority on:

27 October 1999 (27.10.99)

[ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

[ ] was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO **34, chemin des Colombettes** **1211 Geneva 20, Switzerland**	Authorized officer J.M. Vivet
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Form PCT/IB/331 (July 1992)

2985556

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PATENT COOPERATION TREATY

09/647327
5000

From the INTERNATIONAL BUREAU

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NOTIFICATION OF THE RECORDING OF A CHANGE

(PCT Rule 92bis.1 and Administrative Instructions, Section 422)

To:

CORNISH, Kristina
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29 September 2000 (29.09.00)

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IMPORTANT NOTIFICATION

International application No.
PCT/GB99/00966

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26 March 1999 (26.03.99)

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PCT/GB99/00966

PATENT COOPERATION TREATY

5060
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From the INTERNATIONAL BUREAU

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NOTIFICATION OF THE RECORDING OF A CHANGE

(PCT Rule 92bis.1 and Administrative Instructions, Section 422)

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31 October 2000 (31.10.00)

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26 March 1999 (26.03.99)

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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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(54) Title: POLYMORPHISM II: LINKAGE OF ASTHMA TO A LOCUS ON CHROMOSOME 4

(57) Abstract

A method for diagnosing an individual as being asthmatic, or as having a predisposition to asthma is described, which method comprises demonstrating in the individual the presence or absence of one or more alleles which are associated with asthma, wherein the one or more alleles are situated at a locus in a region of chromosome 4 of up to 1 megabase in length, which region contains the locus D4S3032 and/or D4S2921.

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POLYMORPHISM II: LINKAGE OF ASTHMA TO A LOCUS ON CHROMOSOME 4

This invention is concerned with methods for the diagnosis of asthma and with materials and methods relating thereto.

Asthma is a disease which is becoming more prevalent and is the most common disease of childhood (1). Most asthma in children and young adults is initiated by IgE mediated allergy (atopy) to inhaled allergens such as house dust mite and cat dander. However, not all asthmatics are atopic, and most atopic individuals do not have asthma, so that factors in addition to atopy are necessary to induce the disease (2,3). Asthma is strongly familial, and is due to the interaction between genetic and environmental factors. The genetic factors are thought to be variants of normal genes ("polymorphisms") which alter their function to predispose to asthma.

Asthma may be identified by recurrent wheeze and intermittent air flow limitation. An asthmatic tendency may be quantified by the measurement of bronchial hyper-responsiveness in which an individual's dose-response curve to a broncho-constrictor such as histamine or methacholine is constructed. The curve is commonly summarised by the dose which results in a 20% fall in air flow (PD20) or the slope of the curve between the initial air flow measurement and the last dose given (slope). Asthma is accompanied by blood eosinophilia, and eosinophils are prominent in asthmatic airways.

In the atopic response, IgE is produced by B-cells in response to allergen stimulation. These antibodies coat mast cells by binding to the high affinity receptor for IgE (FcεRI). When a multivalent allergen binds to an IgE-coated mast cell, the cross-linking of adjacent IgEs by allergen initiates a series of cellular events leading to the destabilisation of the cell membrane

and release of inflammatory mediators. This results in mucosal inflammation, wheezing, coughing, sneezing and nasal blockage.

Atopy can be diagnosed by (i) a positive skin prick test in response to a common allergen; (ii) detecting the presence of specific serum IgE for allergen; or (iii) by detecting elevation of total serum IgE.

Genetic factors underlying a disease may be identified through localisation to particular chromosomal regions by genetic linkage. Genetic linkage is established by the study of families. It relies on matching the inheritance of disease with genetic polymorphisms of known localisation (known as "genetic markers"). In a complex disease such as asthma, genetic linkage will typically localise genes to within 10 - 20 Megabases (Mb) of DNA. A region of this size may contain 350 - 700 genes, and will be too large to permit immediate identification of the disease-causing gene.

Closer localisation of disease-causing genes may be accomplished by the detection of associations between particular alleles and the disease phenotype. Over short segments of DNA, distinctive alleles of the individual polymorphisms will show non-random association with alleles of neighbouring polymorphisms. This phenomenon, known as "linkage disequilibrium" occurs over 50-500 Kilobases (Kb) of DNA. Linkage disequilibrium may be detected by the study of individuals as well as by the study of families.

Disease-causing alleles will be in linkage disequilibrium with non-functional polymorphisms from the same chromosomal segment. It is therefore possible to detect allelic association with disease from particular chromosomal segments, without identifying the exact polymorphism and gene underlying the disease state.

The detection of allelic association may therefore give information as to disease susceptibility in a particular individual. Furthermore,

allelic association is indicative of a disease-causing gene being present within 500 Kb of DNA in either direction from the allele (i.e. 1 Mb in total). Such a region may contain only 30 genes, within which the identification of the disease-causing gene is possible.

The presence of linkage disequilibrium also means that other polymorphisms may be anticipated to associate with disease, and that these additional polymorphisms will also be diagnostic of disease susceptibility in particular individuals.

Genetic associations with atopy have been demonstrated. WO 95/05481 discloses that variants of the gene encoding the β-subunit of the high-affinity receptor for IgE (FcεRIβ) are associated with atopy. It teaches a method for diagnosing atopy which is based upon the demonstration of the presence or absence of one of two variants in a specific portion of the DNA sequence of the gene encoding FcεRIβ, located near the commencement of exon 6 of the FcεRIβ gene on chromosome 11. A further variant has also been found in which the unusual variant sequence is in the coding sequence for the C-terminal cytoplasmic tail of FcεRIβ (4).

Tumour Necrosis Factor (TNF) is a pro-inflammatory cytokine that is found in increased concentration in asthmatic airways (5). We have previously shown that polymorphisms within the TNF gene are associated with an increased risk of asthma (6).

The known polymorphisms do not account for all of the genetic factors which predispose to asthma. In particular, asthma is not necessarily an atopic disease. Identification of further genetic polymorphisms linked to asthma will allow the identification of children at risk of asthma before the disease has developed (for example immediately after birth), with the potential for prevention of disease. The presence of particular polymorphisms may predict the clinical course of disease (e.g. severe as opposed to mild) or the

response to particular treatments. This diagnostic information will be of use to the health care, pharmaceutical and insurance industries.

We have previously established linkage of bronchial hyper-responsiveness to chromosome 4 (8). However, this finding is of no use in diagnosis.

It has now been discovered that a genetic polymorphism known as D4S3032*5 on chromosome 4 and a nearby polymorphism known as D4S2921*13 are associated with asthmatic traits. Specifically, D4S3032*5 is associated with bronchial hyper-responsiveness and D4S2921*13 is associated with peripheral eosinophilia, both of these being traits which underlie asthma. The two polymorphisms can therefore be used as diagnostic tools.

The invention therefore provides a method for diagnosing an individual as being asthmatic, or as having a predisposition to asthma, which method comprises demonstrating in the individual the presence or absence of one or more alleles which are associated with asthma, wherein the one or more alleles are situated at a locus in a region of chromosome 4 of up to 1 megabase in length, which region contains the locus D4S3032 and/or D4S2921.

The 1Mb region of chromosome 4 referred to flanks the D4S3032 and D4S2921 loci. Thus, the specific allele D4S3032*5, or D4S2921*13, or other unusual polymorphisms in the region which are associated with asthma, may be the subject of identification in the method according to the invention. Equally two or more such alleles may be the subject of identification, including in particular the combination of D4S3032*5 and D4S2921*13.

Current diagnostic methods involving detection at the nucleic acid level normally comprise the steps of:

(i) obtaining a suitable tissue sample from the individual;

(ii) preparing from the tissue sample a nucleic acid sample;

(iii) analysing the nucleic acid sample for the presence or absence of the relevant nucleic acid sequence, such as a specific allele.

Preferably, an amplification step is performed prior to the analysis, such that the locus at which the allele is situated is amplified. A preferred amplification technique is the PCR, although any suitable method of nucleic acid amplification may be employed.

In further aspects, the invention provides a pair of oligonucleotide primers for amplification of an allele which is associated with asthma, which allele is situated at a locus in a region of chromosome 4 of up to 1 megabase in length, which region contains the locus D4S3032 and/or D4S2921; and an assay kit comprising the pair of oligonucleotide primers.

The specific allele for identification may take the form of microsatellite repeats, which are nucleotide sequences containing short, repeated nucleotide motifs, usually a dinucleotide or a trinucleotide motif. A pair of primers which hybridize under suitably stringent conditions, to sequences at a position on either side of the microsatellite repeats, may be used to amplify the microsatellite repeats by PCR. Differences in the number of repeats are recognised by size differences in the PCR products. An allele which has a specified number of repeats and therefore a known size can thus be identified. D4S3032*5 and D4S2921*13 are examples of such alleles.

The primers employed in the method comprise nucleic acid sequences which are complementary to, or substantially complementary to unique sequences either side of the microsatellite repeats, such that only the relevant polymorphic region of the genome is amplified. The conditions under which the amplification is performed are gauged such that specific

hybridization of the primers to the flanking sequences occurs and non-specific hybridization is avoided. The hybridization conditions are suitably stringent for that purpose. Standard techniques can be used to identify an appropriate set of reaction conditions.

Typically, the PCR products are detected by means of a detectable label attached to one of the PCR primers. Alternatively another form of labeling may be used such as a labeled sequence specific probe which hybridizes to the amplified sequences. The label may be a fluorescent or other label. The PCR products are subjected to size determination, typically involving size-separation for example by gel electrophoresis, and the presence or absence of the allele of interest is determined.

It will be evident that the invention is not limited with regard to the manner in which the presence or absence of the allele of interest is determined. The labeling, detection, separation or any other aspect of the method as described here may be replaced by other suitable known techniques and reagents.

The allele for identification may be an allele other than D4S3032*5 or D4S2921*13 which is in linkage disequilibrium with D4S3032*5 or D4S2921*13 and is associated with asthma. This includes alleles of both functional and non-functional polymorphisms. Functional polymorphisms include polymorphisms within genes, usually within coding sequences of genes. Non-functional polymorphisms are polymorphisms which do not themselves cause the disease.

This invention will now be further described in the Examples section which follows. The Examples are intended to be illustrative and do not limit the scope of the invention in any way.

EXAMPLES

Description of Laboratory Testing

Subjects

Two panels of subjects have been studied.

Panel A consisted of 80 nuclear families sub-selected from an Australian population sample of 230 families (8). The panel contained a total of 203 offspring forming 172 sib-pairs. 12% of the children were asthmatic.

Panel C consisted of 87 nuclear families recruited through a child attending an asthma clinic in the Oxford region. The families contained 216 offspring (148 sibling pairs), of whom 44% were asthmatic.

Phenotyping

Bronchial responsiveness to methacholine was measured as previously described (8): the maximum dose administered was 12 μmol. The slope of the dose-response curve was calculated as (pre-dose forced expiratory volume in one second (FEV1) - last FEV1) ÷ the cumulative dose of methacholine). A constant of 0.01 was added to each measurement, to allow $\log_e$ transformation when Slope was ≤ 0. Eosinophils in peripheral blood were Coulter-counted and the values $\log_e$ transformed before analysis.

Genotyping

The microsatellite markers D4S3032 and D4S2921 were typed by semi-automated fluorescent methods, as described previously (8). These markers are in close proximity at the telomeric region of the long arm of chromosome 4.

The polymerase chain reaction primer sequences for the markers were as follows:

D4S3032 5' TGA AAT TCT ATT GAC CAA TGA TGT G (SEQ ID NO: 1)

UD4S3032 5' TAG CAC CTG GAT TTA CCA TGA C (SEQ ID NO: 2)

D4S2921 5' TCC TTC AGG AAC TGG TG (SEQ ID NO: 3)

UD4S2921 5' TTA AAA ATC TAC AGA CAA GGG C (SEQ ID NO: 4)

The polymerase chain reaction conditions were as follows: The reaction volumes were 10µl, containing 50ng of genomic DNA, 200mM dNTPs, 1 x NH4+ buffer, 50ng oligonucleotide primers (forward labelled fluorescently), 0.5 to 3.0mM $MgCl_2$ and 0.2U Taq polymerase. Cycling conditions were 1 min at 95°C, 1 min at 55°C and 45s at 72°C; 28 cycles were used. PCRs were performed on an Hybaid Omnigene thermal cycler.

Electrophoresis and allele scoring were as follows:

PCR products were mixed with a size standard (GS350 TAM) in loading buffer (80% (v/v) formamide, 20% (v/v) 50mM EDTA, 0.1% (w/v) blue dextran). Samples were denatured at 95°C for 4 min immediately prior to loading onto a 6% polyacrylamide gel and were electrophoresed at 800v for 6h on an Applied Biosystems (ABI) 313 DNA sequencer. Allele sizes were assigned using the ABI GENESCAN and ABI GENOTYPER software.

Association Analysis

Association was tested against the phenotype of bronchial hyper-responsiveness and peripheral blood eosinophil counts by the ASSOC routine of the SAGE (ver2.2) computer program.

Results

Association with D4S3032 allele 5 and D4S2921 allele 13

Each of the markers was then tested for association with the asthma phenotype. Association was seen in panel A for allele 5 of D4S3032

(D4S3032*5) and bronchial hyper-responsiveness. This allele is 145 base pairs in size, using the primers described above. Association between allele 13 of D4S2921 (D4S2921*13) and eosinophil counts were seen in both panels. This allele is 162 base pairs in size, using the primers described above. (Other suitable primers can be designed and their amplification product size determined for D4S3032*5 or D4S2921*13, using known sequence information (9).) The results of testing were as follows:

			Panel A		Panel C		Combined	
Trait	Marker	Allele	χ^2	p	χ^2	p	χ^2	p
Slope	d4s3032	5	13.56	0.0002	-	-	-	-
Eosinophils	d4s2921	13	5.00	0.03	11.17	0.0008	17.61	0.0000

The recombination fraction between D4S3032 and D4S2921 was 3%, indicating in this telomeric region that the distance between the markers is of the order of 0.5 to 1 megabase.

The results indicate that D4S3032*5 and D4S2921*13 show strong association with intermediate phenotypes underlying asthma in two diverse panels of subjects. It may therefore be inferred that a gene influencing asthma is present within 500 kilobases in either direction of D4S3032 and D4S2921.

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CLAIMS

1. A method for diagnosing an individual as being asthmatic, or as having a predisposition to asthma, which method comprises demonstrating in the individual the presence or absence of one or more alleles which are associated with asthma, wherein the one or more alleles are situated at a locus in a region of chromosome 4 of up to 1 megabase in length, which region contains the locus D4S3032 and/or D4S2921.

2. The method according to claim 1, wherein the method comprises the steps of:

(i) obtaining a suitable tissue sample from the individual;

(ii) preparing from the tissue sample a nucleic acid sample;

(iii) analysing the nucleic acid sample for the presence or absence of the allele.

3. The method according to claim 2, wherein prior to analysis, the locus at which the or each allele is situated is amplified.

4. The method according to claim 3, wherein the amplification is by the PCR.

5. The method according to any one of claims 1 to 4, wherein the locus at which the or each allele is situated comprises microsatellite repeats of variable length.

6. The method according to claim 3 or claim 4, wherein the amplification is performed using a pair of primers for each allele, wherein each primer in a pair hybridises under suitably stringent conditions to a region either side of the microsatellite repeats.

7. The method according to any one of claims 1 to 6, wherein the allele for identification is D4S3032*5.

8. The method according to any one of claims 1 to 6, wherein the allele for identification is D4S2921*13.

9. The method according to any one of claims 1 to 6, wherein the alleles for identification are D4S3032*5 and D4S2921*13.

10. The method according to any one of claims 3 to 9, wherein the analysis is carried out by size separation of amplification products.

11. The method according to claim 10, wherein the primers in the pair of primers comprise the oligonucleotide sequences identified by SEQ ID NO: 1 and SEQ ID NO: 2 or substantially similar sequences, for D4S3032*5; or identified by SEQ ID NO: 3 and SEQ ID NO: 4 or substantially similar sequences, for D4S2921*13; or both of the aforementioned pairs of primers for both of the aforementioned alleles.

12. A pair of oligonucleotide primers for amplification of an allele which is associated with asthma, which allele is situated at a locus in a region of chromosome 2 of up to 1 megabase in length, which region contains the locus D4S3032 and/or D4S2921.

13. The pair of oligonucleotide primers according to claim 12, one of which is labeled with a detectable marker.

14. The pair of oligonucleotides according to claim 12 or claim 13, capable of hybridising under suitably stringent conditions to a region either side of a region of microsatellite repeats at D4S3032 or D4S2921.

15. The pair of oligonucleotide primers according to claim 14, comprising the oligonucleotide sequences identified by SEQ ID NO:1 and SEQ ID NO:2 or substantially similar sequences, for D4S3032*5; or the oligonucleotide sequences identified by SEQ ID NO: 3 and SEQ ID NO:4 or substantially similar sequences, for D4S2921*13.

16. An assay kit which comprises the pair of oligonucleotide primers according to any one of claims 12 to 15.

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB 99/00966

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C12Q1/68

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C12Q

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	MARONE G: "Asthma: recent advances" TRENDS IMMUNOLOGY TODAY, vol. 19, no. 1, January 1998 (1998-01), pages 1-5, XP004101456 page 1, paragraph 2 ---	1
A	ABRAMSON M ET AL: "The new asthma genetics and its implications for public health" PUBLIC HEALTH REVIEW, vol. 26, no. 2, February 1998 (1998-02), pages 127-144, XP002110731 see abstract and page 137, para 4 to page 138 --- -/--	1-16

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
29 July 1999	10/08/1999

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB 99/00966

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	DANIELS S ET AL: "A genome-wide search for quantitative trait loci underlying asthma " NATURE, vol. 383, 1996, pages 247-50, XP002110730 cited in the application the whole document	1-16
A	WO 95 05481 A (ISIS INNOVATION LTD.) 23 February 1995 (1995-02-23) cited in the application the whole document	1-16
A	DIB C ET AL: "A comprehensive genetic map of the human genome based on 5264 microsatellites" NATURE, vol. 380, 14 March 1996 (1996-03-14), pages 152-154, XP002110732	

INTERNATION[redacted]ARCH REPORT

Information on patent family members

[redacted]International Application No
PCT/GB 99/00966

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9505481 A	23-02-1995	NONE	